



Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

REC'D 23 DEC 2004

WIPO

PCT

Bescheinigung

Certificate

Attestation

Die angehefteten Unterla-
gen stimmen mit der
ursprünglich eingereichten
Fassung der auf dem näch-
sten Blatt bezeichneten
europäischen Patentanmel-
dung überein.

The attached documents
are exact copies of the
European patent application
described on the following
page, as originally filed.

Les documents fixés à
cette attestation sont
conformes à la version
initialement déposée de
la demande de brevet
européen spécifiée à la
page suivante.

BEST AVAILABLE COPY

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03024844.7

**PRIORITY
DOCUMENT**
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1 (a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk



PCT/EP2004 / 052725

Anmeldung Nr:
Application no.: 03024844.7
Demande no:

Anmeldetag:
Date of filing: 31.10.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

ALTANA Pharma AG
Byk-Gulden-Strasse 2
78467 Konstanz
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Novel use of BH4

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

A61K38/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

Novel Use of BH4

Technical Field of the Invention

The invention relates to a novel use of Tetrahydrobiopterin (BH4) or derivatives thereof in the treatment of COPD.

Prior Art

The reduction of endothelium-dependent vasodilatation is mainly induced by a decreased bioavailability of the endothelium-dependent vasodilator nitric oxide (NO) and an increase in the activity of toxic oxygen free radicals such as superoxide anions acting as vasoconstrictors.

It is known from prior art that Nitric Oxide Synthases (NOS: nNOS (NOS1), iNOS (NOS2) and eNOS (NOS3)) produce both NO and superoxide anions. The key in the net outcome of NO production by NOS seems to be the presence of Tetrahydrobiopterin (BH4).

BH4 is an essential co-factor of NOS as it influences the rate of NO vs. superoxide production by NOS [Werner-Felmayer G et al. (2002) Current Drug Metabolism 3: 159]. In conditions when BH4 is reduced, a NOS produces superoxide anions instead of NO [Vasquez-Vivar et al. (1998) PNAS 95: 9220]. NO is rapidly deactivated by superoxide anions resulting in the formation of vasotoxic peroxynitrite (ONOO⁻). In the presence of the toxic oxide radicals, i.e. superoxide anion and ONOO⁻, BH4 is degraded to BH2. BH2 does not act as co-factor for NOS and negatively influences NOS activity [Landmesser et al. J Clin Invest (2003) 111: 1201]. In parallel, ONOO⁻ uncouples NOS so that NOS produces superoxide anion instead of NO. In the endothelium, NO plays a central role in vasodilatation whereas superoxide leads to vasoconstriction. The degradation of BH4 and the uncoupling of NOS and the resulting reduced NO concentration in the endothelium lead to vasoconstriction and finally to hypertension.

It is known from prior art that BH4 plays a key role in a number of biological processes and pathological states associated with neurotransmitter formation, vasorelaxation, and immune response [Werner-Felmayer G et al. (2002) Current Drug Metabolism 3: 159]. As an example deficient production of BH4 is associated with "atypical" phenylketonuria [Werner-Felmayer G et al. (2002) Current Drug Metabolism 3: 159] and provides the basis for endothelial dysfunction in atherosclerosis, diabetes, hypercholesterolaemia and smoking [Tiefenbacher et al. (2000) Circulation 102: 2172, Shinozaki et al (2003) J Pharmacol Sci 91: 187, Fukuda et al (2002) Heart 87: 264, Heltzer et al (2000) Circulation 86: e36].

It is also known in the art that BH4 improves endothelial dysfunction and thereby increases the availability of NO and decreases the presence of toxic radicals. BH4 has a beneficial effect for endothelial function caused by its cofactor role for NOS [Werner-Felmayer G et al. (2002) Current Drug Metabolism 3: 159].

As known from prior art, BH4 and its use as a medicament has been associated with several diseases. According to Ueda et al. [Ueda S et al. (2000) J. Am. Coll. Cardiol. 35:71], BH4 can improve endothelial-dependent vasodilatation in chronic smokers. According to Mayer W. et al. [Mayer W. et al. (2000) J. Cardiovasc. Pharmacol. 35: 173] coronary flow responses in humans are significantly improved by application of BH4. WO9532203 refers to the use of NOS-inhibitory pteridine derivatives ("anti-pterines") for the treatment of diseases caused by increased NO levels. In particular, in accordance with WO9532203, inhibitory pteridine derivatives are described for prevention and treatment of pathological blood pressure decrease, colitis ulcerosa, myocardial infarction, transplant rejection, Morbus Alzheimer, epilepsy and migraine. EP0908182 refers to pharmaceutical compositions comprising BH4 or derivatives thereof for prevention and/or treating of diseases associated with dysfunction of NOS. And EP0209689 refers to the use of tetrahydrobiopterins in the preparation of a medicament for the treatment of infantile autism.

The use of BH4 or derivatives thereof for prevention or treatment of COPD is not known from prior art.

Summary of the invention

Present invention refers to the use of BH4 or derivatives thereof for the prevention and/or treatment of respiratory diseases. In particular, present invention refers to the use of BH4 or derivatives thereof in the prevention and/or treatment of COPD. Surprisingly, it has been found that BH4 or derivatives thereof are beneficial in prevention and/or treatment of a perfusion-ventilation mismatch in respiratory failure and particularly beneficial in the prevention and/or treatment of COPD.

In a first embodiment there is provided the use of BH4 or derivatives thereof for the manufacture of a medicament for the prevention and/or treatment of respiratory diseases.

In a further embodiment of present invention there is provided the use of BH4 or derivatives thereof for the manufacture of a medicament for the prevention and/or treatment of a disease selected from the group consisting of COPD, bronchial asthma, pulmonary fibroses, emphysema, interstitial pulmonary disorders and pneumonias.

In a further embodiment of present invention there is provided the use of BH4 or derivatives thereof for the manufacture of a medicament for the prevention and/or treatment of COPD.

In a further embodiment of present invention there is provided the use of BH4 or derivatives thereof for the manufacture of a medicament for the prevention and/or treatment of muscular dysfunction in COPD patients.

In a further embodiment of present invention there is provided the use of a pharmaceutical preparation comprising BH4 or derivatives thereof for the prevention and/or treatment of COPD.

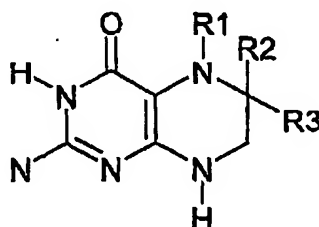
In a further embodiment of present invention there is provided a method for preventing and/or treating COPD in a patient in need thereof comprising the step of administering BH4 or derivatives thereof.

In a further embodiment of present invention there is provided a commercial product comprising a customary secondary packaging, a primary packaging comprising a pharmaceutical preparation of BH4 or a derivative thereof and, if desired, a package insert, the pharmaceutical preparation being suitable for prevention and/or treatment of COPD in patients in need thereof.

Detailed Description of the Invention

Subject of present invention is a new medicinal use of BH4 or derivatives thereof in the treatment of respiratory diseases with underlying pulmonary and extra-pulmonary alterations. The invention thus relates to the use of BH4 or derivatives thereof in the manufacture of a medicament for the prevention and/or treatment of respiratory diseases, in particular in the prevention and/or treatment of COPD.

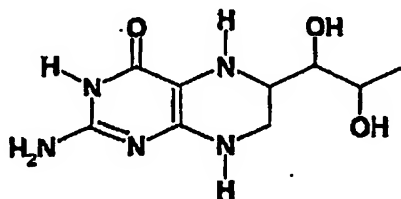
The term "BH4" (tetrahydrobiopterin) refers to all natural and unnatural stereoisomeric forms of tetrahydrobiopterin which has the following formula:



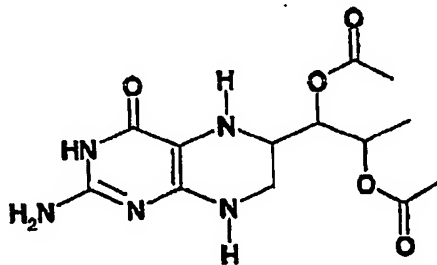
wherein R1 and R2 each represents a hydrogen atom or, taken together with each other, represent a single bond, while R3 represents -CH(OH)CH(OH)CH₃, -CH(OCOCH₃)CH(OCOCH₃), -CH₃, -CH₂OH, or a phenyl group when R1 and R2 each represents a hydrogen atom, or -COCH(OH)CH₃ when R1 and R2 together represent a single bond, or a pharmaceutically acceptable salt thereof.

"BH4 or derivatives thereof" that may be usefully employed in present invention include the compounds as revealed in EP0908182 and EP0079574.

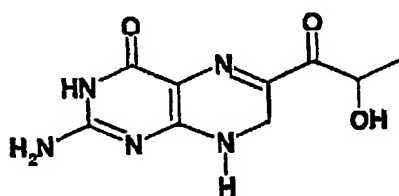
Particular mention is made to the following compounds:



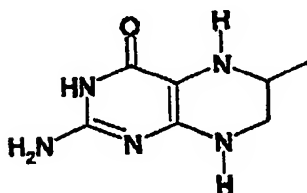
[(6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (BH4)],
(6R,S)-5,6,7,8-tetrahydrobiopterin,



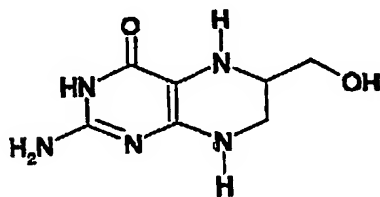
[1', 2'-diacetyl-5,6,7,8-tetrahydrobiopterin],



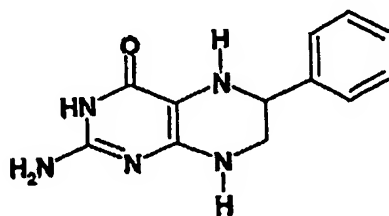
[Sepiapterin],



[6-methyl-5,6,7,8-tetrahydrobiopterin],



[6-hydroxymethyl-5,6,7,8-tetrahydrobiopterin],



[6-phenyl-5,6,7,8-tetrahydrobiopterin],

and the pharmaceutically acceptable salts of these compounds.

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds which are generally prepared by reacting a free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. Particular mention may be made of the pharmaceutically acceptable inorganic and organic acids customarily used in pharmacy. Those suitable are in particular water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)-benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 1-hydroxy-2-naphthoic acid, the acids being employed in salt preparation – depending on whether it is a mono- or polybasic acid and depending on which salt is desired – in an equimolar quantitative ratio or one differing therefrom.

As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

It is understood that the active compounds and their pharmaceutically acceptable salts mentioned can also be present, for example, in the form of their pharmaceutically acceptable solvates, in particular in the form of their hydrates.

The term "respiratory diseases" refers to pulmonary diseases with an underlying partial and global respiratory failure, i.e. with an impairment of oxygen uptake or carbon dioxide release in the lung.

In the healthy lung of humans both at rest and during exercise there are always areas of good and poor or absolutely no ventilation existing simultaneously side by side (ventilation inhomogeneity). An as yet unknown mechanism ensures that there is little or no perfusion of the capillaries adjacent to alveoli with little or no ventilation. This occurs in order to minimize inefficient perfusion of areas of the lung which are not involved in gas exchange. During bodily exercise, the distribution of ventilation changes (recruitment of new alveoli) and there is increased perfusion of the relevant capillary bed. Conversely, when there is less ventilation due to physiological or pathological processes (airway obstruction), the capillary flow are reduced through vasoconstriction. This process is referred to as hypoxic vasoconstriction (Euler-Liljestrand mechanism).

When this adaptation mechanism of ventilation and perfusion is impaired ("mismatch"), there may, despite adequate ventilation and normal perfusion of the lungs, be a more or less pronounced collapse of the gas exchange function, which can be compensated only inadequately despite a further increase in ventilation or perfusion. Under these conditions there are regions which are not ventilated but are well perfused (shunting) and those which are well ventilated but not perfused (dead space ventilation).

The consequences of this "ventilation/perfusion mismatch" are hypoxemia (deterioration in gas exchange with decrease in the oxygen content of the patient's blood), wasted perfusion (uneconomical perfusion of unventilated areas) and wasted ventilation (uneconomical ventilation of poorly perfused areas).

The cause of "partial and global respiratory failure" is inadequate adaptation of the intrapulmonary perfusion conditions to the inhomogeneous pattern of the distribution of ventilation. The resulting mismatch derives from the effect of vasoactive (inflammatory) mediators which prevail over the physiological adaptation mechanism. This effect is particularly evident during exercise and when the oxygen demand is increased and it is manifested by dyspnoea (hypoxia) and limitation of body performance.

"Partial respiratory failure" according to the invention relates to a fall in the O_2 partial pressure in the blood as a manifestation of the aforementioned impairment of oxygen uptake or carbon dioxide release.

According to this invention, "global respiratory failure" relates to a fall in the O_2 partial pressure in the blood and a rise in the CO_2 partial pressure in the blood as a manifestation of the aforementioned impairment of oxygen uptake or carbon dioxide release.

In patients with inflammatory and degenerative lung disorders such as, for example, chronic obstructive pulmonary disease (COPD), bronchial asthma, pulmonary fibroses, emphysema, interstitial pulmonary disorders and pneumonias there is observed to be partial or global respiratory failure. Thus, according to this invention, the term "patient in need thereof" refers to a patient suffering from at least one of the following clinical conditions: COPD, bronchial asthma, pulmonary fibroses, emphysema, interstitial pulmonary disorders or pneumonias.

The term "COPD" is the abbreviation for chronic obstructive pulmonary disease. Patients suffering from COPD are characterized by pulmonary alterations as well as extra-pulmonary alterations such as limited body performance. Pulmonary alterations are changes of airways obstructed due to inflammation, mucus hypersecretion and changes of pulmonary vessels. The resulting limited airflow and the loss of respiratory epithelium results in impaired oxygenation. In addition, pulmonary blood circulation is impaired due to vascular remodeling [Santos S et al. Eur Respir J 2002 19: 632-8] and due to a ventilation/perfusion mismatch deriving from the effect of vasoactive (inflammatory) mediators prevailing over the physiological adaptation mechanism and in part from structural changes of the lung capillaries which develop during the disease progression. This effect is particularly evident during exercise and when the oxygen demand is increased and it is manifested by dyspnoea (hypoxia) and limitation of body performance.

It has now been found, surprisingly, that BH4 is suitable for the treatment of patients with partial and global respiratory failure. According to this invention, in the endothelium, dysregulation of NOS and the

increase of ONOO⁻ concentration both lead to oxidation of BH₄ and thus to reduced BH₄ concentration in the lungs and in skeletal muscle. Reduced BH₄ concentrations result in uncoupling of NOS (iNOS and eNOS) and in an increase in superoxide concentration and finally in the production of ONOO⁻. An increase in superoxide anion concentration leads to more ONOO⁻ and the resulting increase in ONOO⁻ leads to less BH₄ in the lungs and in the skeletal muscle. This circle of superoxide and ONOO⁻ production as well as BH₄ inactivation finally results in endothelial dysfunction and in a ventilation/perfusion mismatch. The administration of BH₄ leads to a re-coupling of NOS (i.e. NOS produce NO instead of superoxide anions), to a reduced generation of superoxide anions and ONOO⁻ and consequentially to an increase in NO which inter alia results in vasodilatation.

The term "prevention and/or treatment of respiratory diseases" as well as "prevention and/or treatment of partial or global respiratory failure" and therewith the term "prevention and/or treatment of COPD" refers to the circumstance that the administration of BH₄ leads to dilatation of vessels in the pulmonary circulation and, at the same time, to a redistribution of the blood flow within the lung in favor of the well-ventilated areas. This principle, referred to hereinafter as rematching, leads to an improvement in the gas exchange function both at rest and during physical exercise in the lungs in patients suffering from partial or global respiratory failure, such as COPD patients. Rematching does not only result in an improved gas exchange in the lungs but also in improved gas exchange in skeletal muscles and therefore in an improvement of physical performance. The term "prevention and/or treatment of muscular dysfunction in COPD patients" exactly refers to this positive outcome of the administration of BH₄ in COPD patients.

BH₄ or derivatives thereof can be administered by any appropriate route known to the person skilled in the art. The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), intranasal, inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurized aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular administration) although the most suitable route may depend upon for example the condition and disorder of the recipient.

The therapeutic agent of the present invention can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route of administration is the oral route. Another preferred route of administration is by way of inhalation of BH₄ or derivatives thereof.

In case of pharmaceutical compositions, which are intended for oral administration, the therapeutic agent is formulated to give medicaments according to processes known per se and familiar to the person skilled in the art. The therapeutic agent is employed as medicament, preferably in combination with suitable pharmaceutical carrier, in the form of tablets, coated tablets, capsules, emulsions, suspensions, syrups or solutions, the therapeutic agent content advantageously being between 0.1 and 95% by weight and, by the appropriate choice of the carrier, it being possible to achieve a pharmaceutical

administration form precisely tailored to the therapeutic agent(s) and/or to the desired onset of action (e.g. a sustained-release form or an enteric form).

The person skilled in the art is familiar on the basis of his/her expert knowledge which carriers or excipients are suitable for the desired pharmaceutical formulations. In addition to solvents, gel-forming agents, tablet excipients and other active compound carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or permeation promoters and complexing agents (e.g. cyclodextrins).

Formulations for inhalation include powder compositions, which will preferably contain lactose, and spray compositions which may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurized packs, with the use of a suitable propellant, e. g. 1, 1, 1, 2-tetrafluoroethane, 1, 1, 1, 2, 3, 3, 3-heptafluoropropane, carbon dioxide or other suitable gas. A class of propellants, which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise hydrofluorocarbons and a number of medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777, W091/04011, W091/11173, W091/11495, W091/14422, W093/11743, and EP 0553298. These applications are all concerned with the preparation of pressurized aerosols for the administration of medicaments and seek to overcome problems associated with the use of this new class of propellants, in particular the problems of stability associated with the pharmaceutical formulations prepared. The applications propose, for example, the addition of one or more of excipients such as polar cosolvents (e.g. alcohols such as ethanol), alkanes, dimethyl ether, surfactants (including fluorinated and non-fluorinated surfactants, carboxylic acids such as oleic acid, polyethoxylates etc.) or bulking agents such as a sugar (see for example WO02/30394). For suspension aerosols, the active ingredients should be micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the aerosol formulation, thus the active ingredients will have a particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 1 to 10 microns, for example, 1 to 5 microns.

It is clear to the person skilled in the art that the therapeutic agent is dosed in an order of magnitude customary for the person in need of the treatment, the administration route, the symptoms to be treated and the patient's condition, although the final decision should be made by an attendant physician.

In case of oral administration of a BH4 preparation, it has proven advantageous to administer 1 to 3 tablets of the preparation per day whereby one tablet contains 10 to 500 mg of BH4 or derivatives thereof. Preferably, the preparations according to the invention are administered per application in such an amount that the amount of BH4 or derivatives thereof is between 0,5 and 50 mg per kilogram of body weight per day. As a rule in the long term treatment of chronic respiratory disorders, such as COPD, BH4 or derivatives thereof may be administered 1 to 3 times in a dosage of 10-100 mg over a period of several years. In the treatment of acute episodes of chronic disorders it may be possible to increase the dosage up to 500mg.

Continuous treatment of chronic disorders may also be possible by administer BH4 or derivatives thereof by inhalation or by intravenous or subcutaneous route administration.

In the case of inhalative administration of BH4 or derivatives thereof, the therapeutic agent is formulated in a form known to the person skilled in the art and dosed in an order of magnitude customary for person in need of the treatment. It has been proven advantageous to administer BH4 or derivatives thereof by inhalation in the following application scheme: Preferably, 10 to 1000 mg BH4 are dissolved in sterile water containing 1 % ascorbic acid. The solution is administered using an inhalation device 1 to 3 times per day in such an amount that the final amount of BH4 is between 0,5 and 50 mg per kilogram of body weight per day. It has been proven advantageous to continuously administer BH4 by inhalation 1 to 3 times in a dosage of 10 to 500 mg. In the treatment of acute episodes of chronic disorders it may be possible to increase the dosage in accordance with the experience of the attending physician.

The "secondary packaging", the "primary packaging" comprising the pharmaceutical preparation and the patient pack correspond to what the person skilled in the art would regard as standard commercial product for pharmaceutical preparations of this type. A suitable "primary packaging" is, for example, a blister. In the case of inhalative administration, the term "suitable primary packaging" refers to a vial including BH4 or derivatives thereof, a vial including the sterile water and a suitable device for inhalation. A suitable "secondary packaging" which may be mentioned by way of example is a folding box.

Industrial Utility

Up to now, only tiotropiumbromid has been launched to market as a bronchodilator for the treatment of the symptoms of COPD. Thus, no curative therapy is currently available. The beneficial effect of present invention refers to the use of known compounds, i.e. BH4 or derivatives thereof, with known compound profiles (known side effects, known absorption, distribution, metabolism, and excretion) as a curative therapy for COPD. The treatment of COPD with BH4 or derivatives thereof addresses the impaired oxygenation in COPD patients due to its rematching effect and the inflammatory component of COPD through its recoupling effect on NOS and thus leads to an improvement in oxygenation and an improvement in physical performance of COPD patients.

Examples**Example 1:****Production of an Injectable BH4 Preparation**

To make up a homogenous solution 1,5 g BH4 dihydrochloride, 1,5 g Ascorbic acid, 0,5 g L-cystein hydrochloride and 6,5 g mannitol were dissolved into sterile purified water to make 100 ml, then sterilized, 1 ml aliquot each was dispensed into a vial or ampule, lyophilized and sealed.

Example 2:**Production of an Injectable BH4 Preparation**

Under anaerobic atmosphere 2,0 g of BH4 dihydrochloride was dissolved in sterile deionized water to make up 100 ml, the sterilized and sealed.

Example 3:**Production of a Tablet Preparation**

Ten parts of ascorbic acid and 5 parts of L-cysteine hydrochloride were added to 1 part of polyvinylpyrrolidone which was dissolved in sterilized deionised water before to give a homogenous solution. Then, 10 parts of BH4 dihydrochloride were added to prepare a homogenous solution. This solution was mixed with 58 parts of lactose and 15 parts of microcrystalline cellulose and 1 part of magnesium stearate and tableted.

Patent Claims

1. Use of BH4 or derivatives thereof for the manufacture of a medicament for the prevention and/or treatment of respiratory diseases.
2. The use of BH4 or derivatives thereof as claimed in claim 1, wherein the respiratory disease is selected from the group consisting of COPD, bronchial asthma, pulmonary fibroses, emphysema, interstitial pulmonary disorders and pneumonias.
3. The use of BH4 or derivatives thereof as claimed in claim 1, wherein the respiratory disease is COPD.
4. Use of BH4 or derivatives thereof for the manufacture of a medicament for the prevention and/or treatment of muscular dysfunction in COPD patients.
5. A method for preventing and/or treating COPD in a patient in need thereof comprising the step of administering an effective amount of BH4 or derivatives thereof.
6. Use of a pharmaceutical composition comprising BH4 or derivatives thereof for the prevention and/or treatment of COPD.
7. A commercial product comprising: a customary secondary packaging, a primary packaging comprising a pharmaceutical preparation of BH4 or derivatives thereof and, if desired, a package insert, the pharmaceutical preparation being suitable for prevention and/or treatment of COPD in patients in need thereof.

Abstract

The invention describes the use of Tetrahydrobiopterin or derivatives thereof for the treatment of COPD.

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record.

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER: _____**

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.